(19) [Emblem] PATENT AND TRADEMARK REGISTRY

SPAIN

(11) Publication Number: **ES 2,046,097**
(21) Application Number: **9102379**

(51) International Classification: **A61K 31/19**
A61K 31/52

(12) **PATENT APPLICATION** **A1**

(22) Application Date: **10/28/91**

(43) Date for Publication of Application: **1/16/94**

(45) Date for Publication of Text of Application: **1/16/94**

(71) Applicant(s): ***Laboratorios S.A.L.V.A.T., S.A.***
Gallo 30-36
08950, Esplugues de Llobregat [Province of] Barcelona, Spain

(72) Inventor(s): **Carlos Monserrat Vidal**

(74) Agent: **Eduardo Maria Espiell Volart**

(54) Title: **Method of Preparing an Anti-dysmenorrheal Composition**

(57)Abstract:
Method of Preparing an Anti-dysmenorrheal Composition

This method is original because it consists of combining: (I) Ibuprofen, (II) Dimenhydrinate, (III) Caffeine, and (IV) Diluents, excipients or appropriate vehicles for administering the product in the form of tablets, capsules, granules, or suppositories. As a whole, this composition possesses surprising peripheral analgesic and anti-emetic activity, as well as counteracting uterine spasms. All of these aspects render it a suitable means of treating dysmenorrhea.

DESCRIPTION

The present invention pertains to a method of preparing a suitable anti-dysmenorrheal composition for symptomatic treatment of pain or discomfort which precedes or accompanies menstruation and is frequently considered to be non-pathological. This invention likewise pertains to compositions obtained as a result of the aforementioned method, which are generally intended for being dispensed without a need for a medical prescription.

State of the Art in relation to the Invention

Dysmenorrhea is pain or discomfort associated with menstruation, and a clearly defined cause has not been determined. It affects more than 50% of women, and the percentage rises to 75% among adolescents (primary dysmenorrhea). Pain, which usually affects the head or the back, tends to be accompanied by nausea or vomiting, and it can be sufficiently intense so as to oblige an individual to remain in bed, with resulting absenteeism from jobs, as well as other social problems of various types. Treatment for dysmenorrhea usually consists of attempting to eliminate symptoms by administering drugs which are principally pain-relieving drugs. Nevertheless, the solutions which have been proposed thus far have not offered satisfactory resolution of the problem of dysmenorrhea, especially for women among whom discomfort is chronic or habitual, and who may, as a consequence, experience side effects which are associated with administration of continuous high doses of the previously indicated drugs.

Patent EP 81828 pertains to a combination of the pain-relieving substance ibuprofen with dextromethorphan for treating dysmenorrhea. This patent also claims a combination of the previously cited substances with caffeine as a diuretic. Nevertheless, it does not cite a combination of ibuprofen and caffeine for treating dysmenorrhea. The combined effects of ibuprofen and caffeine have been investigated for other types of pain, however (Consult A.K. Jain *et al.*, *Current Therapeutic Research,* 1988, Volume 43, pages 762-69).

Explanation of the Invention

It has been determined that relatively low doses of a combination of α-methyl-4-(2-methylpropyl)benzene acetic acid, preferably in its racemic form, or ibuprofen (DCI) with dimenhydrinate (DCI) and caffeine (DCI) provide an especially useful form of synergy for treating the symptoms of dysmenorrhea, whereby successful relief of the associated pain and discomfort can be obtained.

Apparently, dimenhydrinate provides sedating and anti-emetic activity which neutralizes a portion of the typical discomfort associated with dysmenorrhea (nausea and vomiting). In addition, ibuprofen is a specific pain-relieving drug which is highly appropriate for dysmenorrhea. Lastly, caffeine, which is an essential component of the mixture, apparently performs a dual role: on one hand, caffeine neutralizes the sedative effects of dimenhydrinate, thereby rendering it possible for a woman affected by dysmenorrhea to avoid losing energy or even to feel mentally stimulated. Moreover, caffeine enhances the pain-relieving effect of ibuprofen, thereby allowing the same analgesic effect with considerably lower doses of ibuprofen. With the dosages which were tested, the three ingredients were properly absorbed orally, and similar average elimination levels were observed. Hence, the synergic effect is adequately maintained during intervals between one administration and the next. In general terms, the composition provides surprising peripheral analgesic activity, along with anti-emetic activity, and blocking of uterine spasms. All of these aspects render it a suitable means of treating dysmenorrhea.

Hence, the present invention pertains to suitable anti-dysmenorrheal compositions for symptomatic treatment of pain or discomfort which precedes or accompanies menstruation, as well as for treating other painful or spasmodic states affecting the uterus, with said compositions consisting of a combination of: (I) α-methyl-4-(2-methylpropyl) benzene acetic

acid or any of its pharmaceutically acceptable salts in a racemic or enantiomerically pure form or as a mixture of stereoisomers; (II) dimenhydrinate; (III) caffeine; and (IV) appropriate diluents, excipients, or vehicles for oral or rectal administration in the form of tablets, capsules, granules, or suppositories, for example. Compositions where the form of α-methyl-4-(2-methylpropyl)benzene acetic acid which is to be used shall consist of the racemic or ibuprofen form are especially preferable.

According to a preferable version of the present invention, α-methyl-4-(2-methylpropyl)benzene acetic acid is used in a composition in a proportion which is between 10% and 80% according to weight, with dimenhydrinate being used in a proportion between 1% and 10%, while the proportion of caffeine is between 2% and 20%. An even more preferable version is a composition where α-methyl-4-(2-methylpropyl)benzene acetic acid is used in a proportion between 30% and 50% according to weight, while the proportion of dimenhydrinate is between 2% and 5%, and the proportion of caffeine is between 5% and 15%. A still better version of the present invention is one where α-methyl-4-(2-methylpropyl)benzene acetic acid is used in a proportion between 35% and 45% according to weight, while the proportion of dimenhydrinate is between 3% and 4%, and the proportion of caffeine is between 8% and 12%. In terms of individual doses intended for oral administration (hard gelatin capsules or tablets), the optimum situation is represented by 200 mg of ibuprofen, 15 mg of dimenhydrinate, and 50 mg of caffeine, between four and six times per day.

Compositions to which the present invention pertain are suitable for rectal administration and, preferably, for oral administration. In the latter instance, common forms of Galenic preparations, especially hard gelatin capsules and tablets, are suitable. For preparing tablets, it is possible to use diluents, excipients, and vehicles which are ordinarily used in pharmacy.

The present invention also pertains to a method for preparing a suitable anti-dysmenorrheal composition for symptomatic treatment of pain or discomfort which precedes or accompanies menstruation, as well as for treating other painful or spasmodic conditions affecting the uterus. This method is original because it consists of combining:
(I) α-methyl-4-(2-methylpropyl)benzene acetic acid or any of its pharmaceutically acceptable salts in a racemic or enantiomerically pure form or as a mixture of stereoisomers; (II) dimenhydrinate; (III) caffeine; and (IV) appropriate diluents, excipients, or vehicles for oral or rectal administration in the form of tablets, capsules, granules, or suppositories, for example. Preferable versions of this method are those where the respective components are combined according to the previously indicated percentages.

This invention is represented by the following examples:

Examples
Example 1
Preparation of Tablets and Gelatin Capsules

A) Ibuprofen is mixed with colloidal silica. The mixture is homogenized within a mixing system or unit, and it is sifted until a powder with a 250 micron grain size is obtained. This powder is moistened within a mixing machine with a water-alcohol solution of polyvinylpyrrolidone until proper distribution of this solution throughout the powdery mass is obtained. Then drying in an oven is performed.

B) Glyceryl monostearate is melted at a temperature of 60° C. Dimenhydrinate which has previously undergone sifting with a sieve whose openings measure 125 microns is then added, and stirring is performed until a suspension which can cool rapidly is obtained. This suspension is allowed to solidify within a refrigerator. Powdering is to be performed subsequently.

C) Preparations (A) and (B) are mixed with excipients and caffeine according to a 10% concentration. The mixture must then be homogenized, and it must be sifted with a sieve whose openings measure 210 microns as a whole. The resulting powder is then transported by suitable machinery so that it may be placed inside capsules, or so that it may undergo compression and compacting.

Example 2

Anti-dysmenorrheal Activity

Ten female volunteers, who were between 20 and 35 years of age, whose backgrounds included severe and recurrent dysmenorrhea, and who had not responded suitably to treatment with ibuprofen in the past, were instructed to use tablets prepared according to Example Number 1 during a period of 36 hours after experiencing their first symptoms of dysmenorrhea, in a proportion of one tablet each six hours. These tablets possessed the following composition: 200 mg of ibuprofen, 15 mg of dimenhydrinate, and 50 mg of caffeine. The experiment was continued for a year, and, at the end of this period, eight of the patients characterized the reduction of uncomfortable symptoms of dysmenorrhea as "very significant," while one patient characterized the reduction as "moderate" and the others characterized it as "non-existent."

CLAIMS

1. A method of preparing a suitable anti-dysmenorrheal composition for symptomatic treatment of pain or discomfort which precedes or accompanies menstruation, as well as other painful or spasmodic conditions affecting the uterus, characterized by the fact that ibuprofen is used in a 40% concentration, that it is mixed with colloidal silica, and that, after sifting by means of a sieve with openings measuring 250 microns, moistening with polyvinylpyrrolidone in a water-alcohol solution shall occur, because dimenhydrinate, which is to be used in a 5% concentration, shall be mixed with melted glyceryl monostearate, and because the two previously indicated mixtures are to be combined with caffeine in a 10% concentration, as well as with excipients.

2. A method according to the preceding Claim, characterized by the fact that it includes combining of: (I) α-methyl-4-(2-methylpropyl)benzene acetic acid or any of its pharmaceutically acceptable salts in a racemic or enantiomerically pure form or as a mixture of stereoisomers; (II) dimenhydrinate; (III) caffeine; and (IV) diluents, excipients, or vehicles for oral or rectal administration in the form of tablets, capsules, lozenges, or suppositories.

3. A method according to Claim Number 2, characterized by the fact that the α-methyl-4-(2-methylpropyl)benzene acetic acid which is used is the racemic form, or ibuprofen.

4. A method according to either of the Claims identified as Number 2 or Number 3, characterized by the fact that α-methyl-4-(2-methylpropyl) benzene acetic acid is used in the aforementioned composition in a proportion of 10% to 80% according to weight, while the dimenhydrinate proportion is between 1% and 10% and the caffeine proportion is between 2% and 20%.

5. A method according to any of the Claims identified as Number 2 to Number 4, characterized by the fact that α-methyl-4-(2-methylpropyl) benzene acetic acid is used in the aforementioned composition in a proportion between 30% and 50% according to weight, while the dimenhydrinate proportion is between 2% and 5% and the caffeine proportion is between 5% and 15%.

6. A method according to any of the Claims identified as Number 2 to Number 5, characterized by the fact that α-methyl-4-(2-methylpropyl) benzene acetic acid is used in the aforementioned composition in a proportion between 35% and 45% according to weight, while the dimenhydrinate proportion is between 3% and 4% and the caffeine proportion is between 8% and 12%.

7. A method according to any of the Claims identified as Number 2 to Number 6, characterized by the fact that the aforementioned composition is prepared in a galenic form for oral administration, as tablets or as hard gelatin capsules.

8. A method according to Claim Number 7, characterized by the fact that the amounts to be used within each measuring unit are 200 mg of ibuprofen, 15 mg of dimenhydrinate, and 50 mg of caffeine.

9. A method according to either of the Claims identified as Number 7 or Number 8, characterized by the fact that the excipients which are to be used are colloidal silica, polyvinylpyrrolidone, and glyceryl monostearate, among others.

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(11) Publication Number: **ES 2,046,097**
(21) Application Number: **9102379**
(22) Date for Submission of Application: **10/28/1991**
(32) Priority Date:

REPORT CONCERNING STATE OF THE ART

(51) **International Classification:**[5] A61K 31/19, 31/52

RELEVANT DOCUMENTS

Category	Documents Cited	Claims Affected
A	CA-A-2020018 (D.L. SIMMONS)	1-9

Category of documents cited:

- ***X:*** Special relevance
- ***Y:*** Special relevance when combined with others in the same category
- ***A:*** Reflects the [present] state of technology
- ***O:*** Pertains to unwritten disclosure
- ***P:*** Published between the priority date and the date for submission of the application.
- ***E:*** Prior document, although it was published after the date for submission of the application

The present report has been prepared:

X For all claims

___ For Claims whose numbers are:

Date for Preparation of Report	Examiner	Page
July 24, 1993	R. Sanchez-Alfonso	1/1